Enhancing and Shaping Immune Responses with GLA-SE

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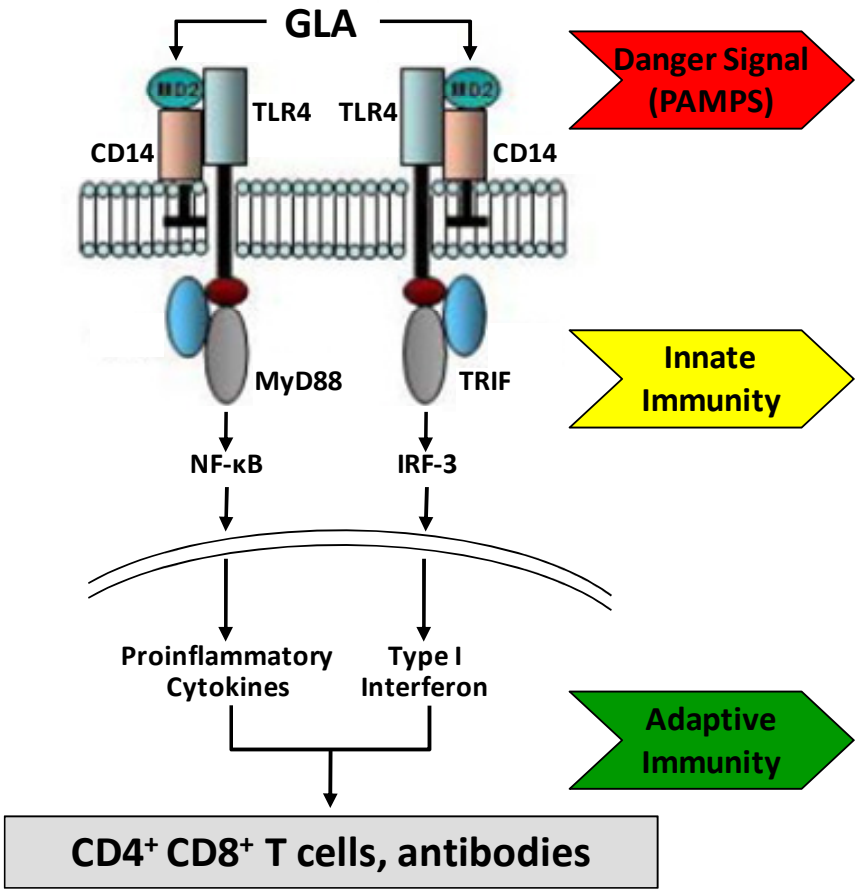
Adjuvants – Critical Component of Next-Generation Vaccines

- Adjuvants are needed to make recombinant protein based vaccines a reality as otherwise they are poorly immunogenic
- Desired Adjuvant Characteristics:
  - Potent immune stimulation
  - Dose sparing effect
  - Response broadening
  - Helps overcome immunoscenescence
  - Excellent safety profile

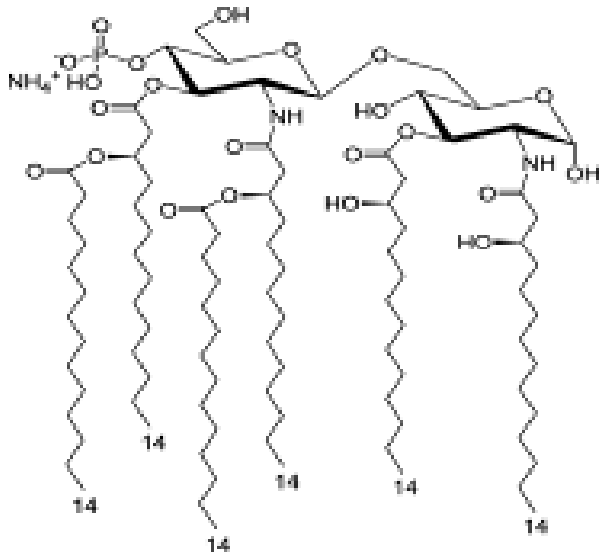


GLA – The First Designer Adjuvant

GLA is a next-generation TLR-4 agonist

- **Designed to optimally activate human TLR-4 receptors**
- **Pure synthetic molecule**
- **Induces Th1 CD4 T helper cells and elicits broad humoral immunity**
- **Straightforward manufacturing and excellent stability**
- **Active in multiple formulations including Stable Emulsion (SE; similar to MF59))**
- **Established safety profile and biologic activity in completed Phase 1 trial**

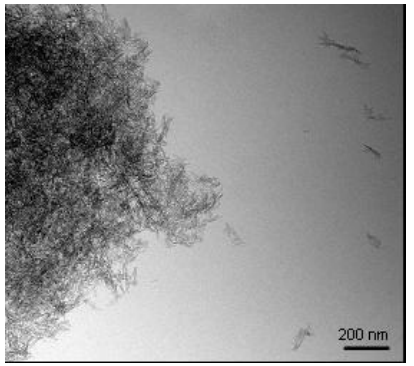
GLA Structure

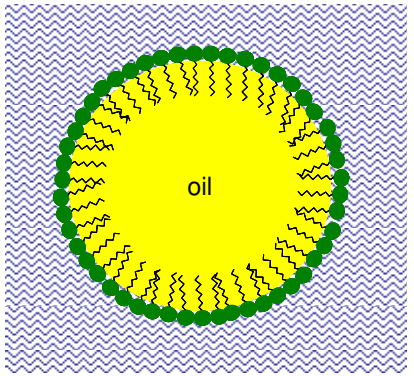


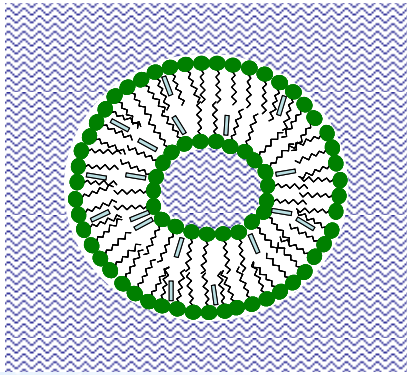
100- to 1000-fold higher potency than MPL

Formulation of GLA

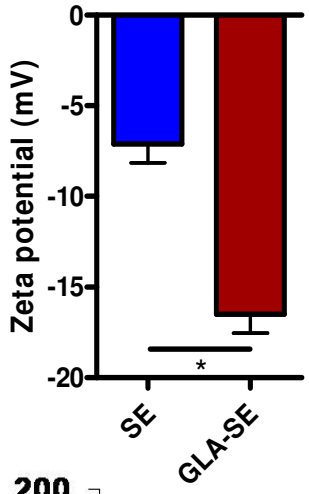
- Aqueous Suspension
  - GLA formulated with lipid excipient, high energy input for nanoparticle production
- Alum
  - GLA adsorbed to aluminum hydroxide gel through electrostatic and/or ligand exchange mechanisms
- Oil-in-water emulsions
  - GLA and lipid emulsifier intercalate at interface of ~100 nm oil droplets
- Vesicles (liposomes, niosomes)
  - GLA intercalates in bilayer of ~100 nm lipid vesicles





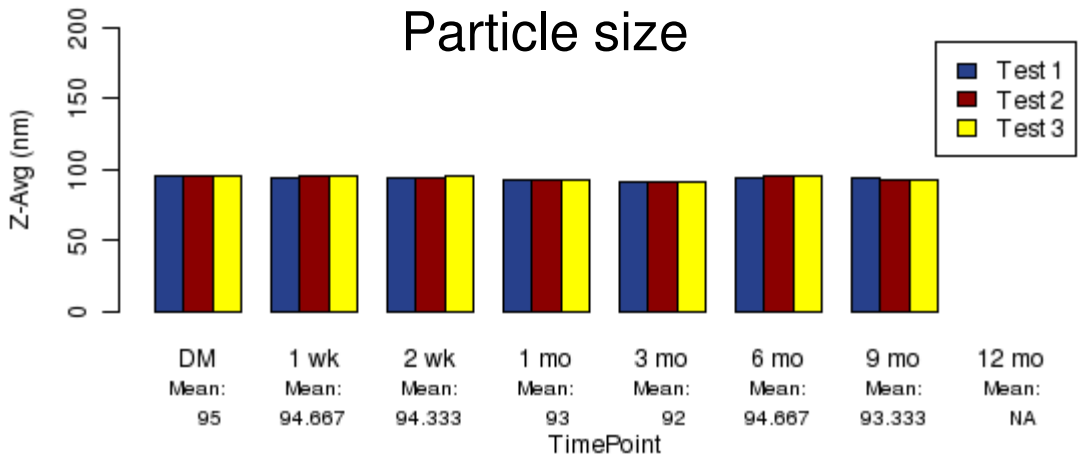


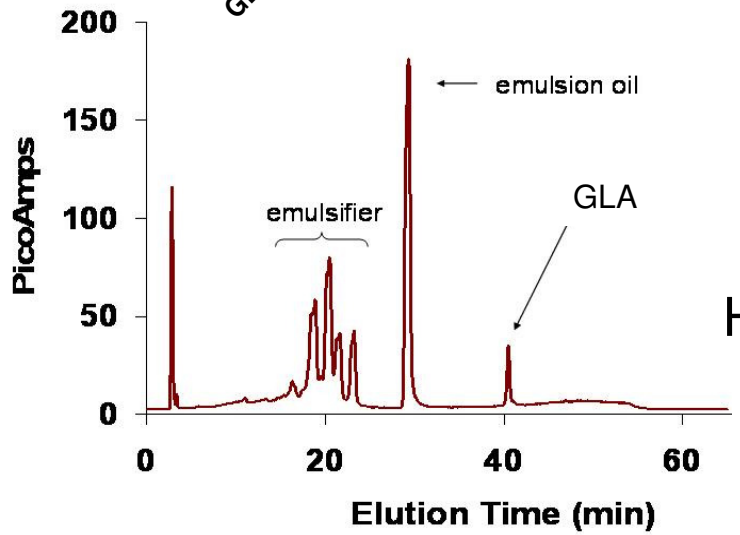
Physicochemical Characterization of GLA-SE



Zeta potential

Particle size

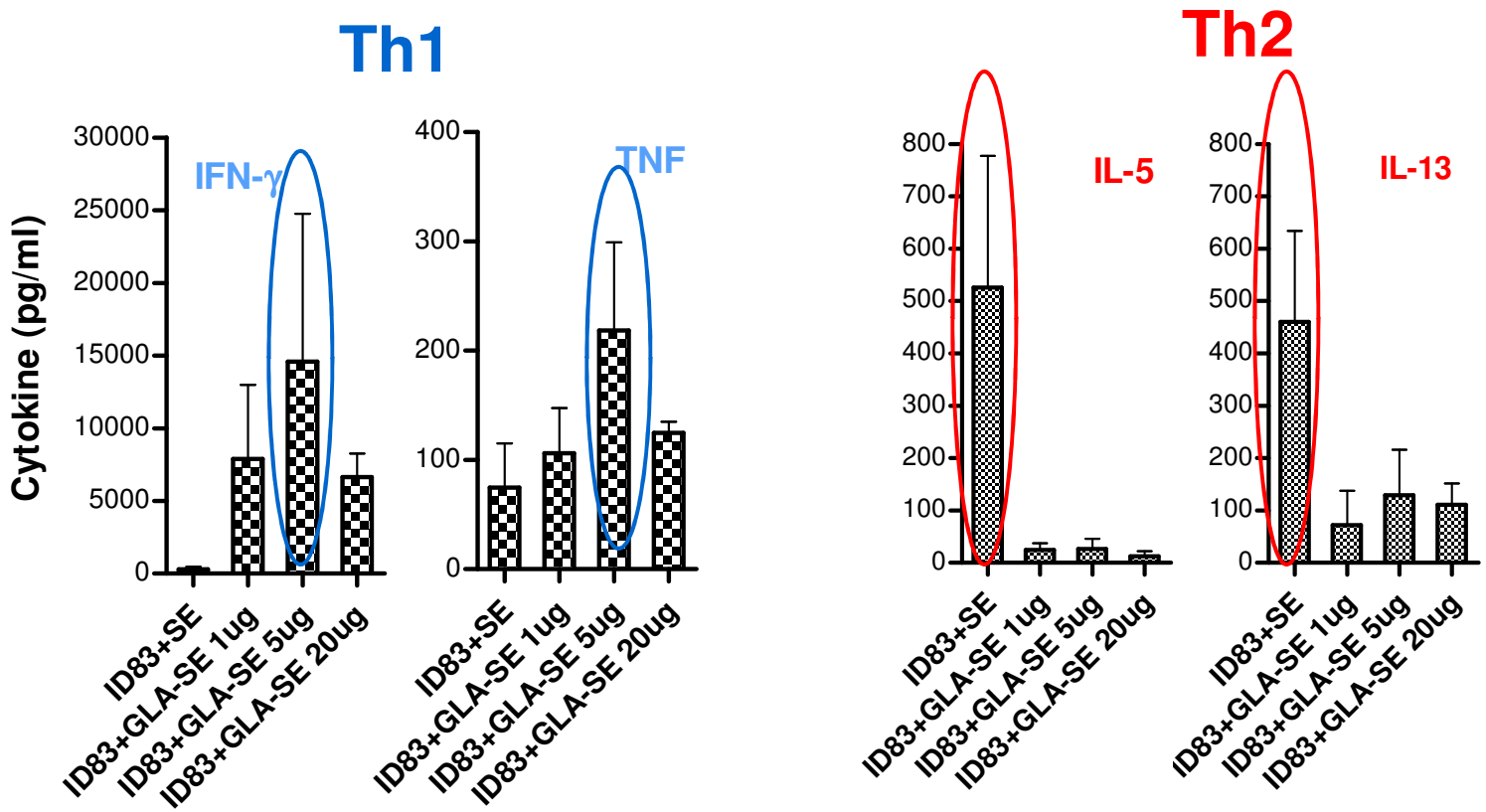




HPLC-CAD

Visual appearance

Shaping the Immune Response: SE vs. GLA-SE; Tuberculosis Vaccine

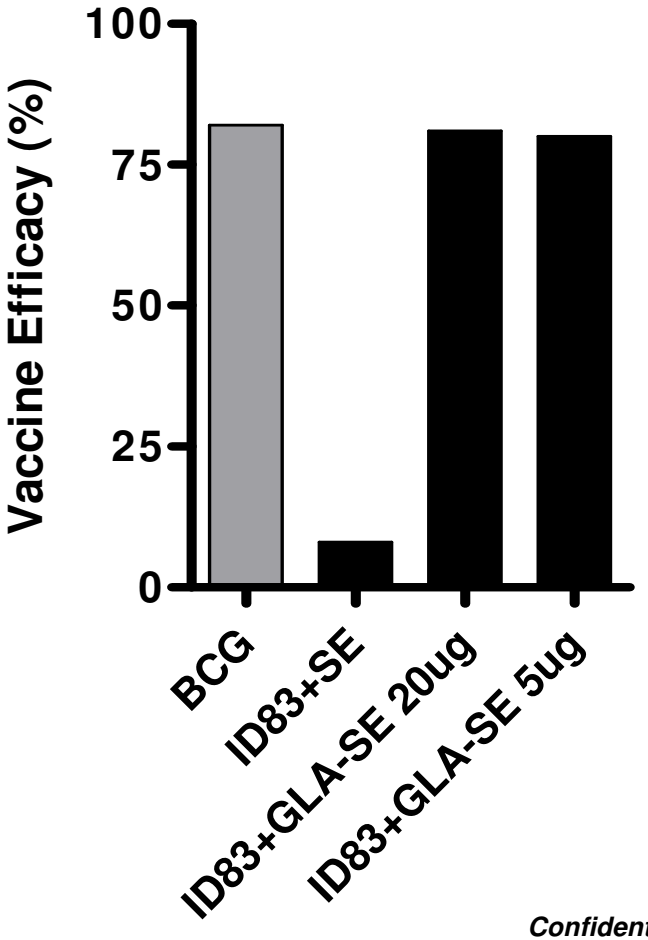


- *GLA-SE enhances Th1 responses while SE promotes Th2 cytokines*

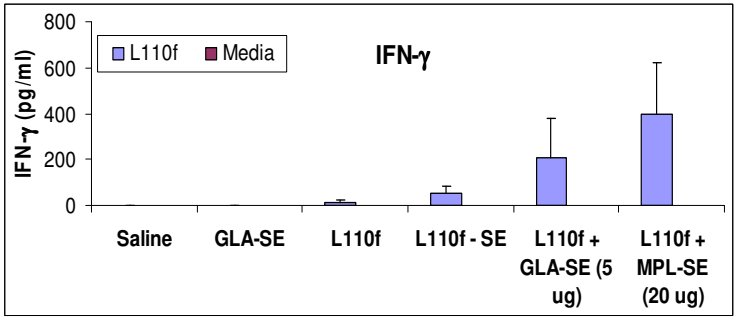
Protective Efficacy of GLA-SE: Tuberculosis

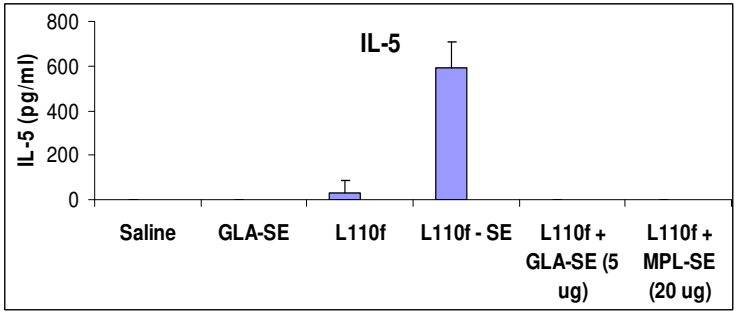
Vaccines	Log10	SD	Log 10 Protection vs Saline	P value vs Saline
Saline	5.81	0.41	0.00	
BCG	5.06	0.31	0.75	P < 0.01
ID83+SE	5.78	0.30	0.04	P > 0.05
ID83+GLA-SE 20 ug	5.09	0.25	0.72	P < 0.01
ID83+GLA-SE 5 ug	5.12	0.29	0.69	P < 0.01

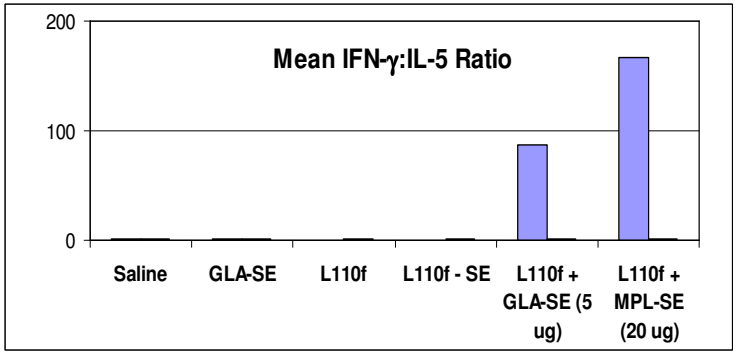
One-way ANOVA followed by Dunnett's Multiple Comparison Test on log-transformed data.

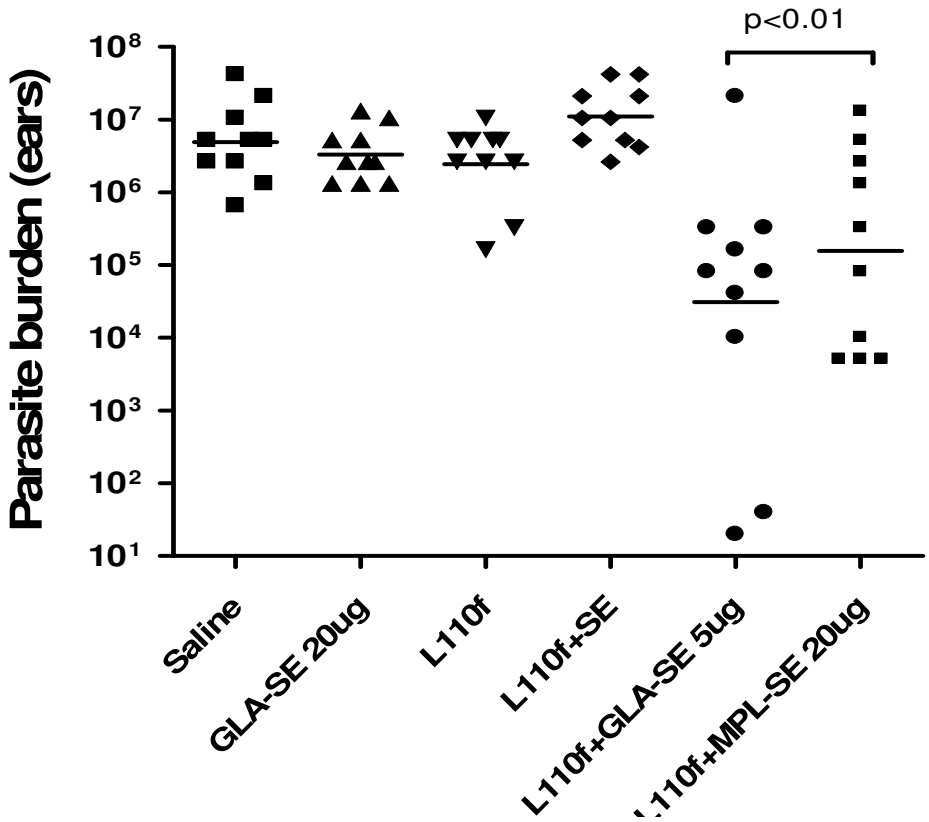


Biological activity of GLA-SE: Leishmaniasis



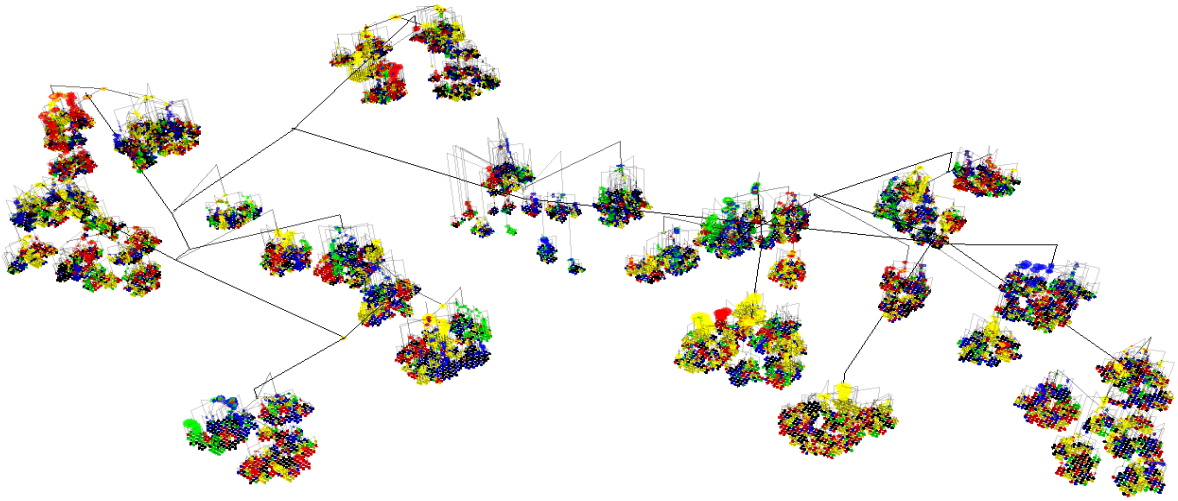


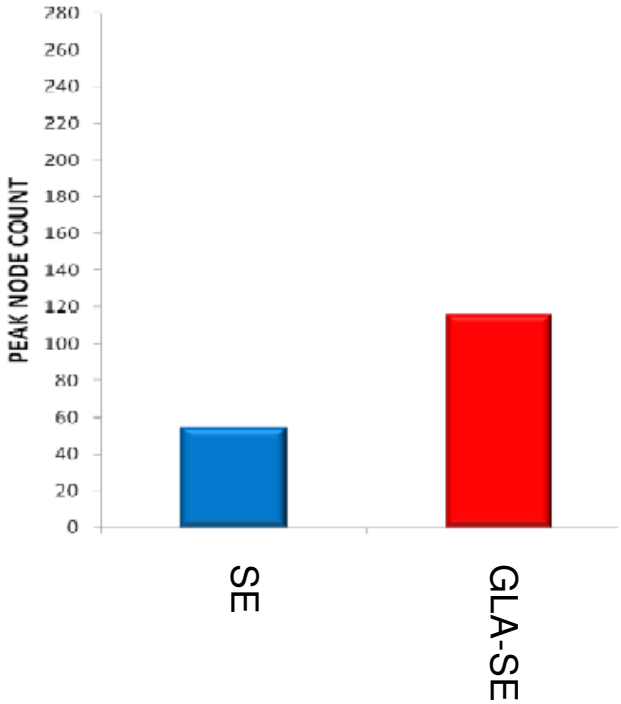




Bertholet et al. Vaccine 2009, 27:7036

GLA-SE Enhances B cell Diversity





- **Deep (Massively Parallel) Sequencing Reveals Enhanced B cell Diversity to a Malaria Antigen (Mice)**

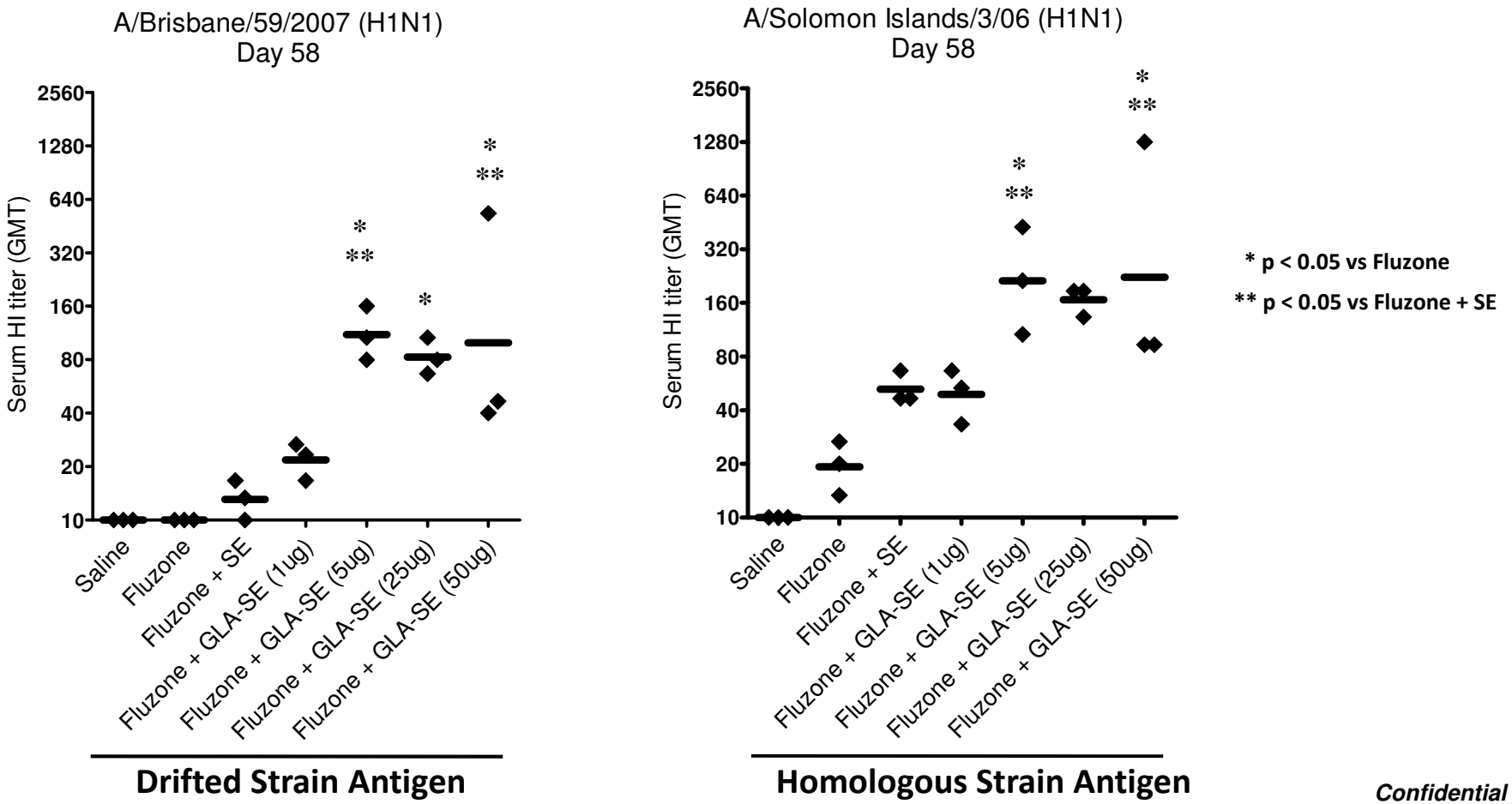
Biological Activity of GLA-SE: Influenza (Fluzone®)

GLA-SE (Stable Emulsion, Oil/Water Formulation)

- **Mouse**
  - **Increases antigen-specific B-cell numbers and antibody production**
  - **Broadens HAI responses with a Th1 bias compared with emulsion alone**
- **Cynomolgus Macaques**
  - **Enhanced sero-conversion rates following a single injection**
  - **Augmented HAI titers > emulsion (SE) alone following a boost vaccination**
  - **Stimulated Th1 T cells and broadens HAI responses to drifted flu strains**

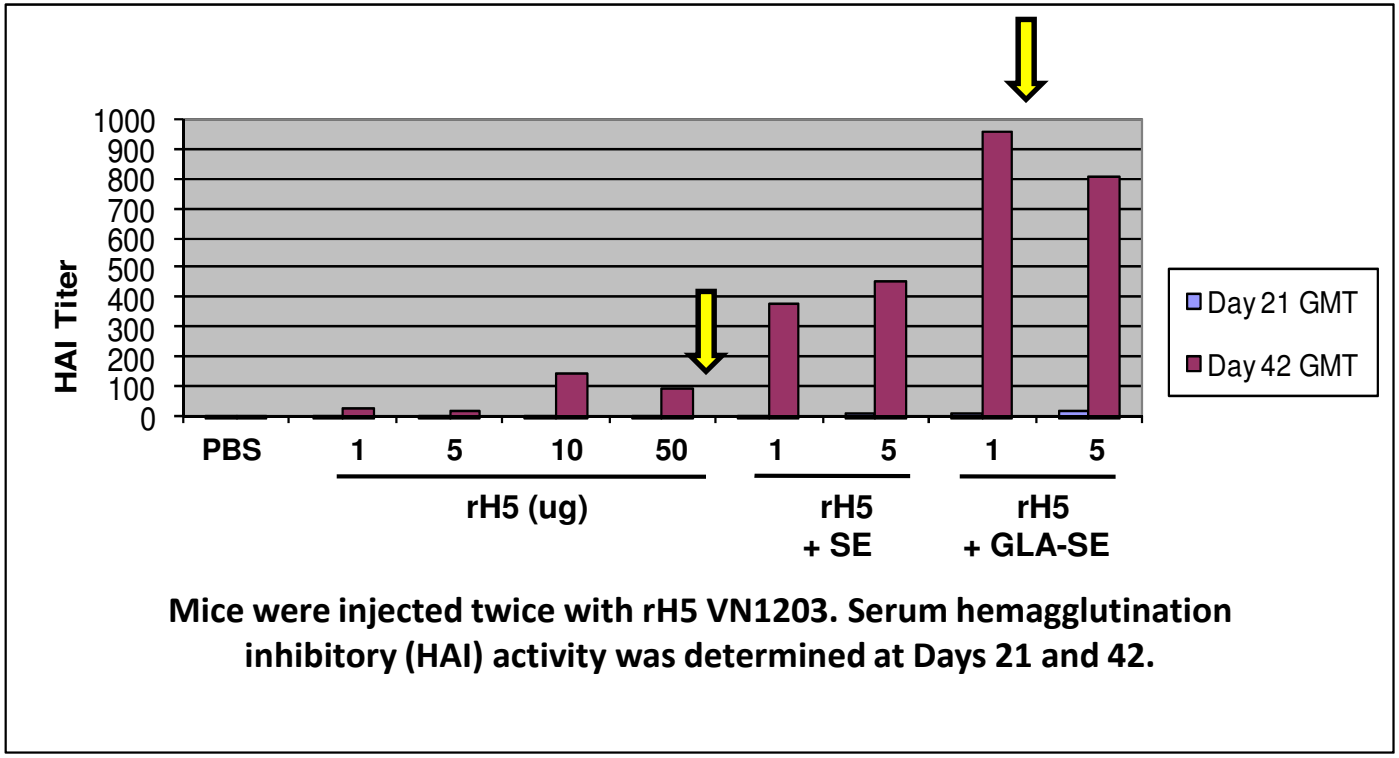
GLA increases and broadens HAI Ab in Cynomolgus Macaques

28 days post second vaccination



GLA-SE – Dose Sparing Effect >50x (rH5N1 Protein Sciences)

GLA-SE augments functional antibody response to H5 avian flu



Mice were injected twice with rH5 VN1203. Serum hemagglutination inhibitory (HAI) activity was determined at Days 21 and 42.

Conclusions

- **GLA-SE induces Th1 CD4 response and broad humoral immunity in various disease models**

- **GLA-SE Adjuvant Provides Significant Dose Sparing of Pandemic (H5N1) Influenza Vaccine (Protein Sciences) as Measured by**
  - **HAI Antibody Titers**
  - **Protection Against Lethal Challenge**

- **Both GLA-SE and SE Effectively Adjuvant rH5N1 Protein for HAI Response, however:**
  - **Significant Dose Sparing Leading to Protection Against Challenge in H5N1 Was Achieved with Antigen Delivered in GLA-SE but not in SE Alone**

- **Solid Protection Achieved in Ferret Model with Range of H5 Doses Formulated in GLA-SE**

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